PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	25 FEB 2005
Applicant's or agent's file reference 30610/30001/	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/00894	10 January 2003 (10.01.2003)	11 January 2002 (11.01.2002)

Applicant

BIOMARINE PHARMACEUTICAL , INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Dr. Kailash C. Srivastava
Facsimile No. (571) 273-8300	Telephone No. 571-272-1600

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 30610/30001/	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/00894	International filing date *(day/month/year)* 10 January 2003 (10.01.2003)	Priority date *(day/month/year)* 11 January 2002 (11.01.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/70, 38/46, 39/395; C07K 1/00; C12P 21/06, 21/04; G01N 33/53 and US Cl.: 424/94.6, 131; 435/7.1, 69.1, 69.7; 514/24, 44; 530/350		
Applicant BIOMARIN PHARMACEUTICAL , INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11 August 2003 (11.08.2003)	14 February 2005 (14.02.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-8300	Authorized officer Dr. Kailash C. Srivastava Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/00894

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-40 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 41-44, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-3, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/00894

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is

☒ complied with.

☒ not complied with for the following reasons:

Group I. Claims 1-13, 14-20 and 27-29
A method to treat a lysosomal storage disease in a subject by administering a pharmaceutical composition comprising a p97 protein conjugate (i.e., compound) and another method to screen for said compound.
Group I.1 Claims 1-13
A therapeutic method to treat a lysosomal storage disease.

I.2 Claims 14-20
A compound (i.e., p97 protein conjugate, Claims 14-20).

I.3 Claims 27-29
Application of said compound in a pharmaceutical composition.

Group II. Claims 21-26.
A second method, i.e. an assay method to screen a compound for therapeutic activity to treat lysosomal storage disease, wherein said compound comprises a p97 covalently linked to a protein.

The inventions listed as Groups I-II do not relate to a single special inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the scope of the product corresponding to the special technical feature is not coextensive for the two methods, i.e., two group of invention do not share a special technical feature.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. ____

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/00894

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-29	YES
	Claims NONE	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-29	NO
Industrial Applicability (IA)	Claims 1-29	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-29 lack an inventive step under PCT Article 33(3) as being obvious over Neuwelt (US Patent 4,866,042) in view of Jeffries et al (US Patent 5,981,194). Neuwelt teaches that the lysosomal storage diseases (e.g., Alzheimer's, Parkinson's, Toy-Sach's) are the result of blood brain barrier (i.e., BBB) because of the genetic disorders causing absence of hydrolases in the lysosomes so that the substrates for those enzymes (e.g., beta-galactosidase, alpha-L-iduronidase) may accumulate (Column 1, Lines 15-68). Neuwelt further teaches a method to treat said diseases through delivering/incorporating directly into the human/subject brain tissue in need thereof, the corrective genetic material or compound comprising the lacking moiety (e.g., a ligand, an enzyme or enzyme substrate). Said material is injected intravenously or intra-arterially, followed by injecting a hyper-osmotic solution of a compound (e.g., mannitol) that temporarily disrupts the BBB (Column 9, Line 30 to Column 10, Line 28; Column 13, Line 25 to Column 14, Line 13). Said material is a pharmaceutical composition because according to Neuwelt it is prepared via inserting the appropriate compound/ human genetic material into a non-infective retrovirus genome, annealing said genome, and closing the vector with a linker that is complimentary to both the vector and the inserted material (Column 8, Lines 29-68; Column 14, Lines 1-30). Prior to injecting said composition in the subject in need thereof, said preparation is screened for therapeutic activity to pass through the BBB via labeling the vector with radioactive sulphur (i.e., (sup.) 35 S). Subsequently a pharmaceutical composition comprising non-labeled said preparation is injected to the subject in need thereof. Because the genome of viral vector together with viral envelope is conjugated to a protein, Neuwelt teaches treating a lysosomal storage disease (e.g., Toy- Sach's) via administering a pharmaceutical composition comprising a protein covalently conjugated to a material whose deficiency causes said disease. The atom chain length for said linker is intrinsically the same as claimed because the prior art teaches a method to prepare a composition comprising same ingredients and steps as claimed instantly. Neuwelt, however, does not clarify that the material administered is a soluble p97 molecule, the linker is polyethylene glycol, or a linking group is 4-20 atom length. Jeffries et al. remedy the deficiency in Neuwelt's teachings by clearly teaching soluble p97 (e.g., Column 6, Lines 21-23) and its application in modulating iron uptake in cells, or controlling binding of p97 to receptors in brain endothelial cells in such manner to treat Alzheimer's, among other diseases (Column 6, Lines 45-57). They further teach a composition for delivering an agent across the BBB comprising p97 in association with a pharmaceutical carrier, wherein p97 is conjugated to the substance to be delivered in a pharmaceutical composition (Column 8, Lines 54-67) via incorporating p97 into vesicles, viral envelopes or cells or DNA to correct defective genetic material (Column 31, Lines 49-67). Jeffries et al. also teach a method to prepare said preparations incorporating p97 and delivering it to the subject in need thereof to diagnose, monitor and treat a lysosomal storage disease, i.e. Alzheimer's (Column 101, Line 25 to Column 102, Line 2).

Thus, at the time, the claimed invention was made, an artisan of ordinary skill would have been motivated to combine the teachings from Neuwelt with the beneficial teachings from Jeffries et al., because Jeffries et al. remedy the deficiency in Neuwelt's teachings of expressly defining the p97, methods to prepare a composition comprising p97 to be delivered to a subject in need of said pharmaceutical composition in diagnosing, monitoring and treating lysosomal storage disease, e.g., Alzheimer's. The actual concentrations of individual components for preparation of said pharmaceutical composition may not be the same as instantly claimed. However, the adjustment of particular conventional working components/ conditions (e.g., types of complimentary materials having same physiological effects and concentrations thereof) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter, which is well within the purview of the skilled artisan. In view of the fact that the applicant's invention also recites composition comprising same components, and methods comprising the same steps and ingredients as are disclosed in prior art teachings; applicant's invention is obvious over the teachings of Examiner-cited prior art references and therefore, lacks an inventive step.

PATENT COOPERATION TREATY

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NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No.	Applicant's or agent's file reference	Date of informal communication *(day/month/year)*
PCT/US03/00894	30610/30001/	08 February 2005 (08.02.2005)
Applicant BIOMARINE PHARMACEUTICAL , INC.		

Communication

☒ by telephone

☐ personal

Participants ☒ Identity checked ☐ authorization checked ☐ personally known

☐ Applicant:

☒ Agent: Ms. Nabeela R. McMillian

☒ Examiner(s): Dr. Kailash C. Srivastava

Summary of communication:

Ms. McMillian (i.e., Applicant's Agent) authorized the Examiner to go directly to International Preliminary Examination Report (i.e., IPER/409).

☐ ~~An extension of time limit is granted (Form PCT/IPEA/427.~~

☒ A copy of this note is being sent to the applicant with Form ~~PCT/IPEA/429.~~ PCT/IPEA/424.

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